ASSOCIATION BETWEEN DISEASE IN THE GALL-BLADDER AND IN THE HEART, AS EVIDENCED AT AUTOPSY†

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The frequent occurrence of cardiac death following operations on the gall-bladder suggested the possibility of some association between cardiac disease and gall-bladder disease. A review of the literature on the subject revealed little definite information. Many clinicians suggest the possibility of such an association, but no definite attempt to establish this has ever been made. The frequent finding of gall-bladder lesions and heart lesions at the post-mortem table suggested the desirability of studying the relation of these two conditions in a large series of post-mortem examinations. A statistical study of the 1600 consecutive autopsies at the New Haven Hospital extending over a period of ten years (from Sept. 21, 1917 to June 11, 1928) was made. These examinations were performed by a large number of individuals, but in each instance the anatomical diagnosis as written by the individual performing the autopsy has been used rather than risk the danger of personal bias in other interpretation.

The methods employed in the present study are based upon those set forth by Yule*. These may be outlined as follows:

Let U be the universe of discourse and $N = (U)$ be the number of individuals in U,

let A be a subclass of U, and let α be a class composed exclusively of those members of U not in A. Then α is called the complement of A. We may express this symbolically by $\alpha = U - A$.

Now, as with U above, we let the class symbol in parenthesis represent the aggregate number of members of the class; *i. e.*,

(A) = number of members of A, and
(α) = " " " " α,

whence $N = (A) + (\alpha)$.

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*G. Udny Yule. *An Introduction to the Theory of Statistics* (1922), pp. 7-59; Charles Griffin and Co., Ltd., London.

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Now, let B be another subclass of U,
and $\beta = U - B$.
Then $(\beta) = N - (B)$.

Now, we employ the symbol A·B to represent* the class whose members are common to both A and B; *i.e.*,
if η is a member of A,
and η is a member of B,
then and only then is η a member of A·B. Then (A·B) is used to represent the number of individuals in A·B.

Now, when $\frac{(AB)}{(B)} > \frac{(A)}{N}$ we say that A is positively associated with B, or simply, that A and B are associated;

when $\frac{(AB)}{(B)} < \frac{(A)}{N}$ we say that A is negatively associated with B, or that A and B are disassociated;

and when $\frac{(AB)}{(B)} = \frac{(A)}{N}$ we say that A and B are unassociated.

A coefficient has been proposed (*cf.* Yule, page 38) defined by the relation

$$Q = \frac{(AB)\ (\alpha\beta) - (A\beta)\ (\alpha B)}{(AB)\ (\alpha\beta) + (A\beta)\ (\alpha B)},$$

which may be written

$$Q = \frac{(UAB)\ (U\alpha\beta) - (UA\beta)\ (U\alpha B)}{(UAB)\ (U\alpha\beta) + (UA\beta)\ (U\alpha B)}.$$

A discussion of this coefficient, Q, is given by Yule, where it is pointed out that for the case of positive association $1 \geqq Q > 0$; for the case of negative association $-1 \leqq Q > 0$; and for the case of no association $Q = 0$.

Now, if $Q = 1$, we say there is complete positive association; and, if $Q = -1$, we say that there is complete disassociation. Obviously, if $Q = 1$, then either $(A\beta) = 0$, or $(\alpha B) = 0$, or both; and if $Q = -I$, then either $(AB) = 0$, or $(\alpha\beta) = 0$, or both; and conversely.

*The notation is that employed in symbolic logic, identical with that in the book of Yule. A·B does not mean a product as in algebra.

If a class symbol contains no Greek letter, it is called (for convenience) a "positive class"; *e.g.*, U, A, B, and A·B are the *positive classes* in the above discourse.

Now, it is possible to express Q in terms of the positive class aggregate numbers alone, as follows:

$$\begin{aligned} (\alpha\beta) &= (\alpha) - (\alpha B), \\ (\alpha) &= N - (A), \text{ and} \\ (\alpha B) &= (B) - (AB), \\ \text{therefore } (\alpha\beta) &= N - (A) - (B) + (AB); \\ \text{and } (A\beta) &= (A) - (AB). \end{aligned}$$

Now, let $J = (AB)\ (\alpha\beta)$, and $K = (A\beta)\ (\alpha B)$;

then, obviously, $Q = \dfrac{J-K}{J+K}$.

But, from the above relations, we have

$$\begin{aligned} J &= (AB)\{N - (A) - (B) + (AB)\} \\ &= N\,(AB) - (A)\,(AB) - (B)\,(AB) + (AB)^2, \\ \text{and } K &= \{(B) - (AB)\}\ \{(A) - (AB)\} \\ &= (A)\,(B) - (A)\,(AB) - (B)\,(AB) + (AB)^2, \end{aligned}$$

whence $J - K = N\,(AB) - (A)\,(B)$,

and $J + K = (AB)\{2\,[(AB) - (A) - (B)] + N\} + (A)\,(B)$;

whence $Q = \dfrac{N\,(AB) - (A)\,(B)}{(AB)\{2\,[(AB) - (A) - (B)] + N\} + (A)\,(B)}$;

whence, if $(AB) = 0$, then $Q = -1$, and if $(AB) \neq 0$,

$$\text{then } Q = \frac{N - \dfrac{(A)\,(B)}{(AB)}}{2\,[(AB) - (A) - (B)] + N + \dfrac{(A)\,(B)}{(AB)}}.$$

The calculation of the coefficient of association of gall-bladder disease and heart disease in the 1600 autopsies studied will serve as an illustration. Here we have

$U = 1600$ specified autopsies, $(U) = N = 1600$,

$(A) = 472 =$ Number of autopsies in U in which a cardiac lesion* was observed,

*This general heart disease class will later be designated by A_1.

(B) = 155 = Number of autopsies in U in which gall-bladder disease was observed and,

(AB) = 75 = Number of autopsies in U in which both a cardiac lesion and gall-bladder disease were observed;

$$\text{whence } Q = \frac{1600 - \frac{(472)\ (155)}{75}}{2(75 - 472 - 155) + 1600 + \frac{(472)\ (155)}{75}}$$

$$= 0.42 \text{ (approx.)}.$$

Thus we find a positive association between gall-bladder disease and heart disease in the 1600 autopsies studied, with a coefficient of 0.42.

In view of this result it appeared that it might be interesting to carry out similar association studies with respect to specialized types of heart disease. In any classification certain attributes which may be called its *critical attributes*, are stated to define the class. The critical attributes of each such class chosen for the present study are given below together with the name and symbol assigned.

A_1—*Heart Disease:* presence of any heart lesion.

A_2—*Arteriosclerotic Heart Disease: (a)* coronary sclerosis, even with a superimposed thrombosis of the coronary arteries, with or without infarcts of the myocardium or mural thrombi, or fibrosis of the myocardium, or *(b)* generalized arteriosclerosis with cardiac hypertrophy, with or without dilatation, even without coronary sclerosis, or *(c)* calcification of the aortic and mitral valves in the presence of other evidence of arteriosclerosis, but with no evidence of endocarditis.

A_3—*Endocarditis: (a)* acute lesions of the valves of the heart, or *(b)* vegetative or verrucous, or healed endocarditis (the last with or without calcification).

A_4—*Myocarditis: (a)* acute or chronic myocarditis (the former including instances manifested chiefly by hemorrhage), or *(b)* abscesses of the myocardium, or *(c)* focal necrosis of the myocardium with foci of infection elsewhere in the body.

A_5—*Syphilitic Heart Disease: (a)* syphilitic mesaortitis with cardiac involvement, or *(b)* gumma of the myocardium.

A_6—*Pericarditis: (a)* purulent or fibrous pericarditis (fibrosis of the pericardium) or hydropericardium without other cardiac disease.

A_7—*Miscellaneous Heart Disease: (a)* brown atrophy of the heart muscles, or *(b)* serous atrophy of the subepicardial fat, or *(c)* "fatty heart", or *(d)* pigmentation of the myocardium following hemochromatosis, or *(e)* congenital malformation of the heart, or *(f)* patent ductus arteriosus persisting beyond 5 weeks of postnatal life, or *(g)* hemorrhage into the media of the ductus arteriosus, or *(h)* defect in the interventricular septum, or *(i)* cardiac dilatation alone, or *(j)* cardiac hypertrophy alone, or with dilatation, or with polycystic kidneys, or *(k)* fibrosis of the myocardium alone, or *(l)* mural or ball thrombi alone, or *(m)* tumors involving the heart, malignant or benign (hemangioma), or *(n)* multiple thrombi in coronary arteries without other coronary disease.

The complements of these classes are

$$\alpha_i = U - A_i, \text{ where } i = 1, 2, \ldots, 7.$$

The gall-bladder disease class, B, contains every individual in the universe of discourse, U, in which was observed:— *(a)* acute or chronic cholecystitis with or without stones, or *(b)* acute cholangeitis, or *(c)* fibrous pericholecystitis, or *(d)* fibrosis and atrophy of the gall-bladder with fistulous communication between the gall-bladder and the duodenum, or *(e)* carcinoma of the bile ducts, or *(f)* chronic pericholangeitis, or *(g)* obstruction of the common bile-duct with dilatation of the gall-bladder.

No attempt has been made to study association with respect to distinct types of gall-bladder disease in the work to be reported at present. The numbers of individuals found in each of these classes is given in Table I, together with the observed value of (A_iB) and the corresponding value of Q in each instance.

TABLE I.

N=1600 (B)=155

	Number of Individuals with						
	Any heart lesion	*Arterio-sclerosis*	*Endocard-itis*	*Myocard-itis*	*Syphilitic Heart Disease*	*Pericard-itis*	*Misc. Heart Disease*
In U	472=(A_1)	137=(A_2)	144=(A_3)	34=(A_4)	27=(A_5)	39=(A_6)	124=(A_7)
In B	75=(A_1B)	33=(A_2B)	26=(A_3B)	0=(A_4B)	2=(A_5B)	4=(A_6B)	13=(A_7B)
Q= Coeff. of Ass. A_1 with B	0.42	0.55	0.41	—1.0	—0.15	0.03	0.05

It appears that there is a significant association between the classes A_1 and B—individuals with heart disease irrespective of type and those with gall-bladder disease. A positive association that is somewhat greater is found between B and A_2—individuals with heart conditions classed as arteriosclerotic. The association between the gall-bladder disease class and the endocarditis class is also positive. On the other hand, in the present experience there is complete disassociation between gall-bladder disease and myocarditis, $Q=-1$. There seems to be little association between gall-bladder disease and the other forms of heart disease mentioned above; namely, syphilitic heart disease, pericarditis, and those classed as miscellaneous.

In order to estimate the significance of the coefficient of association between given attributes it is necessary to calculate the value of Q with respect to the same attributes in several mutually independent universes, n in number which can not be less than 2 and if possible should never be less than 4. In lieu of other universes independent of that already employed, it is permissible for this purpose to divide the universe under consideration into four (preferably equal) mutually exclusive subuniverses, provided no attempt is made to pick the members of any of these subuniverses upon any basis which may be influenced by bias in regard to the associations studied. Thus we may divide the universe of 1600 autopsies into four subuniverses, each of 400 individuals taken consecutively, which may be called U_1, U_2, U_3, U_4, respectively. We may call this an equal division into quarters chronologically. Bases of subdivision other than the chronological may readily be suggested. The present interest, however, is to estimate chronological reproducibility.

An association table for $A_1 \cdot B$, $A_2 \cdot B$, and $A_3 \cdot B$ is given in Table II together with the respective association coefficients in these four subuniverses, and that for the including universe, U. The average *numerical* deviation, λ, of the corresponding coefficients of the subuniverses from that of U is given in each instance in the same table.

TABLE II

	U_1 First 400 Individuals	U_2 Second 400 Individuals	U_3 Third 400 Individuals	U_4 Fourth 400 Individuals	U
Total No. with Gall-bladder Involvement	(U_1B) $=34$	(U_2B) $=45$	(U_3B) $=42$	(U_4B) $=34$	
Total No. with Heart Involvement	(U_1A_1) $=90$	(U_2A_1) $=106$	(U_3A_1) $=133$	(U_4A_1) $=143$	
Total No. with Gall-bladder and Heart Involvement	(U_1A_1B) $=12$	(U_2A_1B) $=22$	(U_3A_1B) $=25$	(U_4A_1B) $=16$	
Q	0.34	0.51	0.55	0.25	0.42 $\lambda=0.12$
Arteriosclerotic Heart Disease	(U_1A_2) $=16$	$U_2A_2)$ $=26$	(U_3A_2) $=43$	(U_4A_2) $=52$	
Gall-bladder and Arteriosclerotic Heart Disease	(U_1A_2B) $=5$	(U_2A_2B) $=10$	(U_3A_2B) $=9$	(U_4A_2B) $=9$	
Q	0.69	0.72	0.46	0.46	0.55 $\lambda=0.12$
Endocarditis	(U_1A_3) $=37$	(U_2A_3) $=33$	(U_3A_3) $=39$	(U_4A_3) $=35$	
Gall-bladder Disease and Endocarditis	(U_1A_3B) $=7$	(U_2A_3B) $=7$	(U_3A_3B) $=10$	(U_4A_3B) $=2$	
Q	0.49	0.40	0.56	−0.23	0.41 $\lambda=0.22$

Note: $Q = \dfrac{(UAB)\ (U\alpha B)-(UA\beta)\ (U\alpha B)}{(UAB)\ (U\alpha B)+(UA\beta)\ (U\alpha B)}$ as before, where Uj, A_i, and B are substituted for U, A, and B respectively.

A value of Q is considered to differ from zero significantly if it is numerically not less than $\dfrac{4\lambda}{\sqrt{n}}$, which in the present circumstances equals 2λ. However, the failure so to qualify as significant in accord with this arbitrary criterion should not be considered as the equivalent of no significance in any but this arbitrary sense, but rather as an indication that further study should precede any definite claim to the contrary.

In Table III will be found the result of a similar subdivision of U according to ten-year age intervals, excluding individuals whose age at death was not stated (21 in number).

TABLE III.

	Age Groups in Years								
	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81+
No. of Autopsies	466	87	163	166	221	191	173	78	31
Arteriosclerotic Heart Disease	0	0	1	7	10	30	48	22	16
Arteriosclerotic Heart Disease in Presence of Gall-bladder Disease	0	0	0	0	1	6	14	8	4
Endocarditis	10	9	23	23	23	22	24	5	4
Endocarditis in Presence of Gall-bladder Disease	0	0	2	3	5	4	8	3	1
Total Gall-bladder Disease	2	0	11	10	19	32	38	27	16

If we calculate the coefficient of association for gall-bladder disease and arteriosclerotic heart disease for the age period wherein the latter is most prevalent, namely, 51 years or more, we obtain the value of 0.12. It appears from this result that the higher coefficient of association for these two classes which is obtained for the entire universe of 1600 autopsies is due principally to the fact that the majority of members of these two classes were over 51 years of age.

The coefficient of association for endocarditis and gall-bladder disease for the age interval (21 to 70 years) in which most of the instances of each occur is 0.31, which is probably best considered as not significantly different from 0.41, as found for the original universe.

In Table IV will be found the data from the division of U according to sex with reference to association between heart and gall-bladder involvement. The agreement between the values of Q obtained is striking in view of the marked divergence in the frequencies themselves.

TABLE IV.

	Total No.	*Individuals with Heart Disease*	*Individuals with Gall-bladder Disease*	*Individuals with Gall-bladder Disease and Heart Disease*	*Q*
Males	964	283	59	29	0.42
Females	633	189	96	46	0.43

SUMMARY.

1. In the series of 1600 autopsies studied there is a significant association between the occurrence of heart disease in general and gall-bladder disease.

2. There is a significant association between gall-bladder disease and arteriosclerotic heart disease in the whole series studied; however there is apparently no significant association between the occurrence of the two lesions in an age period in which most of the instances of each lie.

3. The association between gall-bladder disease and endocarditis in the same universe is positive, but under the present test conditions fails by a slight margin of classification as chronologically significant; and also is positive, but to less degree, in an age period in which most of the instances of each lie.

4. An experience of complete disassociation was observed between myocarditis and gall-bladder disease, but the reproducibility of such experience remains to be tested.

5. In the case of other types of heart disease studied no significant association with gall-bladder disease was found.

6. The coefficient of association between heart and gall-bladder disease is of practically equal magnitude in the case of males and females in the present experience.